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(54) Title: PHARMACEUTICAL FORMULATION COMPRISING AZITHROCYCIN MONOHYDRATE

(57) Abstract: The present invention relates to pharmaceutical orally administrable compositions comprising azithromycin which is stabilized in the form of a monohydrate.

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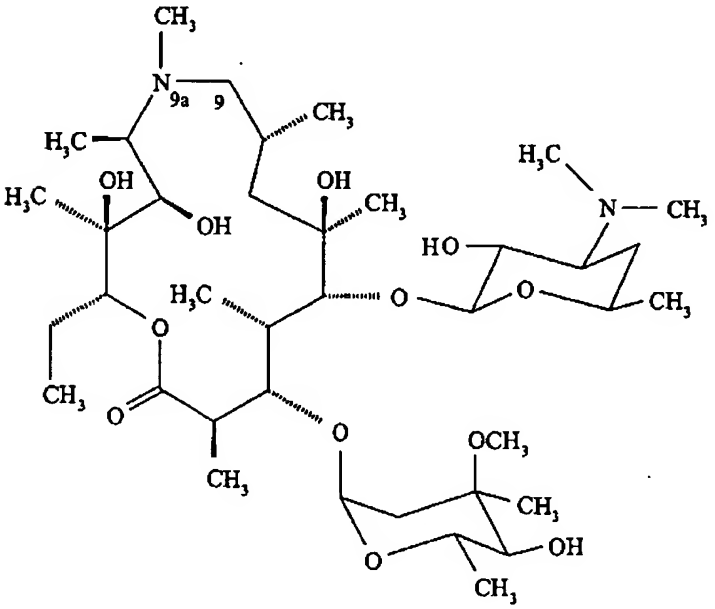
PHARMACEUTICAL FORMULATION COMPRISING AZITHROMYCIN MONOHYDRATE

The present invention concerns pharmaceutical orally administrable compositions comprising a compound of formula



I

characterized in that the compound of formula I is stabilized in the form of a monohydrate. A compound of formula I is known as an antibacterial effective ingredient under the INN azithromycin and is described e.g. in The Merck Index, 11th edition, item 928, page 146. Crystalline azithromycin is known to form solvates such as hydrates, e.g. a dihydrate or a monohydrate. Even though the hydrates of azithromycin do not need to contain a stoichiometric amount of water they can be characterized and distinguished, e.g. by their characteristic powder X-Ray diffraction spectra, as it is described for instance in EP-A-984020 or EP-A-941999.

It is known that azithromycin in the form of a monohydrate may be unstable and may contain undesired degradation products when set out to normal air humidity conditions.

WO 02/42315 discloses a process for the production of azithromycin in the form of a monohydrate which may maintain its crystalline structure shown by its characteristic X-ray powder diffraction pattern during long-term storage, e.g. for at least 2 weeks under normal air and/or humidity conditions. The stable monohydrate form of azithromycin is described to have a stable water content from 4.0% to 6.5% (w/w) of water. If the water content is out of that range, the crystalline structure including the form of solvation of azithromycin may not

be stable and may degrade and/or be converted into undesired different forms, e.g. a dihydrate or an anhydride.

The aim of the present invention is to provide a pharmaceutical orally administrable composition comprising azithromycin wherein said azithromycin is stabilized in the form of a monohydrate. The monohydrate of azithromycin may be obtained according to a process as described in WO01/00640 or in WO 02/42315 and can be characterized, e.g. by X-ray diffractometry or by IR-spectroscopy, e.g. as referenced in EP-A-984020.
Stabilization of the crystalline structure of azithromycin in the form of a monohydrate can be achieved by adjusting the water content in a pharmaceutical orally administrable formulation in order to maintain a water content of the azithromycin of not less than 4% and not exceeding 6.5% based on the weight of azithromycin. If not otherwise stated herein, water content is determined according to the method of Karl Fischer.

The water content of the pharmaceutical orally administrable composition may be adjusted by using auxiliaries with defined water content.
A pharmaceutical orally administrable composition includes any final dosage form of azithromycin for oral administration, such as a dosage form that is ready for direct oral administration to an individual in need thereof.
In one particular aspect of the present invention the orally administrable composition is a capsule or a tablet, e.g. a film coated tablet. A capsule or a tablet may be prepared analogously, e.g. according to known methods as conventional, e.g. by direct compression, dry granulation or wet granulation, provided that the water content is in the range of about 4% to about 8% (w/w) based on the total weight of the composition during the whole process. A tablet may be coated, e.g. by a film or a coating analogously, e.g. according to methods as conventional. A tablet according to the present invention may comprise in addition to azithromycin pharmaceutically acceptable auxiliaries as conventional, such as fillers, binders, thickeners, lubricants, glidants, disintegrants, flavoring agents, taste masking agents etc. A tablet or capsule may comprise an amount of azithromycin in the form of a monohydrate corresponding to an amount of azithromycin as conventional, e.g. from 100 mg to 1000 mg per tablet.
Suitable coating materials include those materials conventionally used in coating tablets, granules and the like. In particular, coating materials suitable for use in the practice of the invention include but are not limited to water-soluble polymer coating materials, such as

cellulose derivatives, e.g. hydroxypropylmethylcellulose (e.g. Opadry), or conventional sugar coatings. The coating may additionally comprise flavoring and/or coloring agents.

Suitable lubricants or glidants includes but are not limited to alkali- or earth alkaline salts of stearic acid and talcum. Suitable fillers and binders includes but are not limited to sugars, celluloses, cellulose derivatives, polyvinylpyrrolidones, starches, starch derivatives. Suitable disintegrants includes but are not limited to starches and modified starches, silica. Suitable thickeners include but are not limited to polysaccharides, starches, starch derivatives and cellulose derivatives.

It has been found that the azithromycin can be stabilized in the form of a monohydrate by maintaining a certain degree of humidity within the pharmaceutical orally administrable composition during the whole process of preparing it. Therefore, a further aspect of the present invention is a tablet or a capsule comprising azithromycin in the form of a monohydrate wherein the water content is in a range from about 4.0%, preferably from about 4.5%, to about 8%, preferably to about 6.5% (w/w) based on the total weight of the composition.
In another aspect the present invention provides a process for preparing a tablet or a capsule comprising azithromycin in the form of a monohydrate wherein all steps are carried out under the provision that the water content of the mixture of active ingredient with auxiliaries is in the range of about 4% to about 8% (w/w) of water.

In another aspect of the present invention the orally administrable composition is a solid that is dissolved or suspended to obtain a solution or suspension for oral administration, e.g. a powder or a granulate. In addition to azithromycin, conventional pharmaceutically auxiliaries such as filler, binders, taste masking agents, lubricants, glidants etc. may be present. Preferably, a powder for an oral suspension comprises from 77% to 98.5 % (w/w) of auxiliaries, including a sugar and from 1% to 20% (w/w) of azithromycin in the form of a monohydrate and has a water content from 0.5% to 3% (w/w) based on the total weight of the composition.
A granulate or a powder for an oral solution or suspension according to the present invention may be prepared analogously, e.g. according to a process as conventional, e.g. dry blending, provided that the water content is always within the range of 0.5% to 3% (w/w) of water based on the total weight of the granules or powder.

A particular aspect of the present invention is a granulate or powder for an oral suspension or solution comprising azithromycin in the form of a monohydrate wherein the water content is in a range from 0.5%, preferably from 0.6% to 3%, preferably to 2.5% (w/w) based on the total weight of the composition. Thus, a further aspect of the present invention is a process for preparing a granulate or a powder for an orally administrable suspension or solution comprising azithromycin in the form of a monohydrate wherein all steps are carried out under the provision that the water content of the mixture of active ingredient with auxiliaries is in the range from 0.5% to 3% (w/w) of water.
The applied energy and/or the drying temperature have to be adjusted in the processes of the present invention to ensure that the water content of the compositions or of the mixtures for preparing the compositions remain in the ranges specified above.

Azithromycin in other crystalline forms, e.g. in the form of a dihydrate or in the form of an anhydride are substantially absent in the pharmaceutical orally administrable compositions of the present invention.

The crystalline structure of azithromycin, i.e. in the form of a monohydrate, has a considerable long-term stability in a pharmaceutical orally administrable composition according to the present invention. There is substantially no degradation in a composition according to the present invention. After at least 2 weeks, e.g. 4 or 6 weeks, under room temperature and humidity conditions such as 70% to 80% relative air humidity, the degradation of azithromycin in the form of a monohydrate is less than 2%, e.g. 0% to 1.8% based on the weight of azithromycin in the form of a monohydrate initially present.

The following Example illustrates the present invention but shall not be interpreted to limit it.

Examples

Example 1:

The compounds of table 1 are mixed. Approximately 50 kg of water are added. The moistened mixture is compressed into tablet cores with an average weight of 850 mg. The tablet cores are coated with 18 mg Opadry AMB OY-B-28920 per each core by spraying a .

Table 1: compounds for preparing tablet cores

component	quantity per batch of 100000 units [kg]
azithromycine monohydrate	51.2
microcrystalline cellulose (Avicel pH 102)	6.0
pregelatinised starch (Starch 1500)	20.2
sodium starch glycolate (Primojel)	4.2
colloidal silica, anhydrous (Aerosil 200)	1.0
sodium lauryl sulfate	0.3
magnesium stearate	2.1

Claims

1. A pharmaceutical orally administrable composition comprising azithromycin characterized in that the azithromycin is stabilized in the form of a monohydrate.
2. A composition according to claim 1 wherein the pharmaceutical composition is a tablet.
3. A composition according to claim 2 wherein the total water content is in the range from 4% to 8% based on total weight of the composition.
4. A composition according to claim 1 wherein the pharmaceutical composition is a powder for oral suspension.
5. A composition according to claim 4 wherein the total water content is in the range from 0.5% to 3% based on total weight of the composition.
6. A process for preparing a tablet or a capsule comprising azithromycin in the form of a monohydrate wherein all steps are carried out under the provision that the water content of the mixture of active ingredient with auxiliaries is in the range of 4% to 8% (w/w) of water.
7. A process for preparing a granulate or a powder for an orally administrable suspension or solution comprising azithromycin in the form of a monohydrate wherein all steps are carried out under the provision that the water content of the mixture of active ingredient with auxiliaries is in the range from 0.5% to 3% (w/w) of water.

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International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/7048

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, SCISEARCH, CHEM ABS Data

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X	WO 02 42315 A (LUDESCHER JOHANNES ;GARCIA RAFAEL (ES); BIOCHEMIE SA (ES); DIAGO J) 30 May 2002 (2002-05-30) cited in the application claim 4 ---	1-7
X	WO 01 00640 A (LUDESCHER JOHANNES ;GARCIA RAFAEL (ES); BIOCHEMIE SA (ES); DIAGO J) 4 January 2001 (2001-01-04) cited in the application claims 8,17 --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Friederich, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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